Amendments to the Claims

The following listing of claims replaces all prior claim listings in the application:

1. (*Currently amended*) A method for combinatorially controlling the transcription of a target ~~genes~~ gene in a cell for producing a programmed response in the cell, the method comprising:

identifying a plurality of logic functions, wherein each logic function combines two or more different inputs to generate an output comprising a unique gene expression in the cell;

implementing at least one selected logic function that produces a desired genetic response when a combination of specified conditions are present, wherein the two or more different inputs comprise two or more regulatory proteins and the at least one selected logic function is implemented by producing interactions between the two or more regulatory proteins and interactive binding of the two or more regulatory proteins at ~~corresponding~~ DNA binding sites of the target ~~genes~~ gene to control a probability of promoter occupancy, wherein the target gene comprises one or more cis-regulatory regions having individual DNA binding sites, and wherein each DNA binding site has a binding strength and a binding location which are adjustable by varying composition of the one or more cis-regulatory regions to select one of a cooperative binding and competitive binding of the two or more regulatory proteins at the binding sites and one of a cooperative binding and competitive binding ~~of~~ between the two or more regulatory proteins ~~with~~ and polymerase;

wherein the interactions comprise contact interactions and long-distance interactions that avoid interference between the DNA binding sites; and

wherein the desired genetic response in the cell comprises reporting or treatment of a disease or condition in which the two or more regulatory proteins are expressed .

2. (*Previously presented*) The method of claim 1, wherein the one or more cis-regulatory regions are modular.

3. (*Original*) The method of claim 1, wherein the at least one logic function is selected from the group consisting of: OR, AND, NAND, XOR and EQ.

4. (*Original*) The method of claim 1, wherein at least some of the interactions among the regulatory proteins comprise non-specific protein-protein interactions controlled by selecting the binding locations.

5. (*Original*) The method of claim 1, wherein at least some of the interactions among the regulatory proteins comprise specific protein-protein interactions.

6. (*Previously presented*) The method of claim 1, wherein at least some of the interactions among the regulatory proteins comprise protein-protein interactions mediated by collaborative competition between the regulatory proteins and a glue-like DNA-bound protein or protein complex.

7. (*Original*) The method of claim 1, wherein the interactive binding comprises tunable-specific protein-DNA interactions which are tunable by selecting the binding strengths.

8. (*Previously presented*) The method of claim 1, wherein the one or more cis-regulatory regions include long distance repression and activation schemes.

9. (*Previously presented*) The method of claim 1, wherein the step of implementing the at least one logic function further comprises:

reducing the at least one logic function to a minimal conjunctive normal form; and

implementing a first clause as an activation clause and all remaining clauses as repression clauses;

wherein the relative binding strength is selected so that repression dominates activation.

10. (*Previously presented*) The method of claim 1, wherein the step of implementing the at least one logic function further comprises:

reducing the at least one logic function to a minimal disjunctive normal form; and

implementing a first clause as a repression clause and all remaining clauses as activation clauses.

11. (*Currently amended*) A method for combinatorial transcription control for controlling gene expression in a cell <u>for producing a programmed response in the cell</u>, the method comprising:

identifying a plurality of logic functions, each logic function having two or more different inputs and an output comprising a unique and artificial genetic response ~~gene expression that does not normally occur under the conditions corresponding to the two or more inputs~~;

selecting at least one logic function that produces a desired genetic response; and

implementing the at least one logic function by producing interactions among different inputs comprising two or more transcription factors and controlling interactive binding of the two or more transcription factors at corresponding binding sites of one or more target genes, wherein the target genes each comprise one or more cis-regulatory regions having individual DNA binding sites, and wherein each binding site has a binding strength and a binding location which are adjustable by varying composition of the one or more cis-regulatory regions to select one of a cooperative interaction and competitive interaction between the two or more transcription factors and to select cooperative or competitive binding ~~of~~ between the two or more transcription factors ~~with~~ and polymerase, all to control a probability of promoter occupancy; and

generating the desired genetic response in the cell as the output, wherein the desired genetic response in the cell comprises reporting or treatment of a disease or condition in which the two or more transcription factors are expressed.

12. (*Previously presented*) The method of claim 11, wherein the one or more cis-regulatory regions are modular.

13. (*Original*) The method of claim 11, wherein the at least one logic function is selected from the group consisting of: OR, AND, NAND, XOR and EQ.

14. (*Original*) The method of claim 11, wherein at least some of the interactions among the transcription factors comprise non-specific protein-protein interactions controlled by selecting the binding locations.

15. (*Original*) The method of claim 11, wherein at least some of the interactions among the transcription factors comprise specific protein-protein interactions.

16. (*Previously presented*) The method of claim 11, wherein at least some of the interactions among the transcription factors comprise protein-protein interactions mediated by

collaborative competition between the transcription factors and a glue-like DNA-bound protein or protein complex.

17. (*Original*) The method of claim 11, wherein the interactive binding comprises tunable-specific protein-DNA interactions which are tunable by selecting the binding strengths.

18. (*Previously presented*) The method of claim 11, wherein the cis-regulatory region includes long distance repression and activation schemes that avoid interference between the DNA binding sites.

19. (*Original*) The method of claim 11, further comprising, after the step of identifying the at least one logic function:

reducing the at least one logic function to a minimal conjunctive normal form; and

implementing a first clause as an activation clause and all remaining clauses as repression clauses;

wherein the binding strength is selected so that repression dominates activation.

20. (*Original*) The method of claim 11, further comprising, after the step of identifying the at least one logic function:

reducing the at least one logic function to a minimal disjunctive normal form; and

implementing a first clause as a repression clause and all remaining clauses as activation clauses.

21. (*Currently amended*) A method of ~~artificially~~ combinatorially controlling gene expression in a cell by encoding control functions in regulatory DNA sequences for producing a programmed response in the cell, the method comprising:

selecting a relative binding strength and a relative binding position of individual DNA binding sites within a cis-regulatory region of one or more regulatory DNA sequences to exert combinatorial control of gene expression to operate as at least one logic function selected from a plurality of different logic functions for combining two or more inputs, each input comprising a different regulatory protein, to generate an output comprising a programmed gene expression upon DNA binding of two or more different regulatory proteins as determined by the selected relative binding strength and relative binding position of the DNA binding sites to control probability of

promoter occupancy, wherein each different logic function produces a different programmed gene expression in the cell; and

wherein the programmed gene expression in the cell comprises reporting or treatment of a disease or condition in which the two or more different regulatory proteins are expressed .

22. (*Original*) The method of claim 21, wherein the control functions are modular.

23. (*Previously presented*) The method of claim 21, wherein the relative binding strengths and relative binding sites within the cis-regulatory region are selected to produce tunable specific DNA-protein interactions and non-specific, glue-like protein-protein interactions.

24. (*Original*) The method of claim 23, further comprising selecting the relative binding strengths and relative binding sites to permit distal activation and repression.

25. (*Currently amended*) A method for combinatorial control of gene expression to produce a programmed genetic response in a cell, the method comprising:

producing a plurality of different glue-like contact interactions between two or more transcription factors at DNA binding sites of genes for selectively activating or repressing expression in a target gene under specified conditions that comprise to inputs into one or more logic functions, wherein the one or more logic functions are selected according to a relationship between the two or more transcription factors and a disease or condition, wherein each DNA binding site has a protein-DNA binding affinity and a binding location that are variable by varying a cis-regulatory sequence at the DNA binding site to select a predetermined combination of degrees of freedom selected from the group consisting of DNA binding thresholds for each transcription factor, Boltzmann weight for promoter occupancy, and mutual cooperativity factors between the transcription factors and RNA polymerase, wherein the predetermined combination of degrees of freedom controls a probability of promoter occupancy ~~produces~~ to produce a desired genetic response in the cell; and

wherein the desired genetic response in the cell comprises reporting or treatment of the disease or condition in which the two or more transcription factors are expressed.

26. (*Currently amended*) The method of claim 25, wherein the ~~predetermined combination~~ one or more logic functions is selected from a group of logic functions consisting of OR, AND,

NAND, XOR and EQ, wherein the two or more transcription factors are inputs to the logic functions and the desired genetic response is the output.

27. (*Previously presented*) The method of claim 25, wherein the cis-regulatory sequence comprises an operator sequence and a promoter sequence, and wherein protein-DNA binding affinity is programmed by selecting the operator sequence while interactions between the two or more transcription factors are programmed by selecting the position of the promoter sequence within the binding site.

28. (*Currently amended*) The method of claim 1, wherein the ~~two or more regulatory proteins are different proteins expressed in~~ disease or condition is cancer ~~cells~~ and the desired genetic response is activation of a reporter gene.

29. (*Currently amended*) The method of claim 1, wherein the ~~two or more regulatory proteins are different proteins expressed in~~ disease or condition is cancer ~~cells~~ and the desired genetic response is activation of a killer gene.

30. (*Currently amended*) The method of claim 1, wherein the ~~two or more regulatory proteins are different proteins expressed in cells subjected~~ disease or condition is exposure to an external chemical or biological agent and the desired genetic response is activation of a reporter gene.

31. (*Currently amended*) The method of claim 1, wherein ~~the two or more regulatory proteins are different proteins expressed in cells of a subject having a disease or condition and the~~ desired genetic response is activation of a drug receptor of a drug for treatment of the disease or condition.

32. (*New*) The method of claim 11, wherein the disease or condition is cancer and the desired genetic response is activation of a reporter gene.

33. (*New*) The method of claim 11, wherein the disease or condition is cancer and the desired genetic response is activation of a killer gene.

34. (*New*) The method of claim 11, wherein the disease or condition is exposure to an external chemical or biological agent and the desired genetic response is activation of a reporter gene.

35. (*New*) The method of claim 11, wherein desired genetic response is activation of a drug receptor of a drug for treatment of the disease or condition.

36. (*New*) The method of claim 21, wherein the disease or condition is cancer and the desired genetic response is activation of a reporter gene.

37. (*New*) The method of claim 21, wherein the disease or condition is cancer and the desired genetic response is activation of a killer gene.

38. (*New*) The method of claim 21, wherein the disease or condition is exposure to an external chemical or biological agent and the desired genetic response is activation of a reporter gene.

39. (*New*) The method of claim 21, wherein desired genetic response is activation of a drug receptor of a drug for treatment of the disease or condition.

40. (*New*) The method of claim 21, wherein the probability of promoter occupancy is determined according to the relationship $P_{po} = \frac{Z_{ON}}{Z_{ON} + Z_{OFF}}$, where Z_{ON} and Z_{OFF} are the total statistical weight of all states in which the promoter is occupied and unoccupied, respectively.

41. (*New*) The method of claim 40, wherein the at least one selected logic function is AND, and $Z_{ON} = q_0(1 + \omega q_A + q_B + 2\omega^2 q_A q_B)$ and $Z_{OFF} = 1 + q_A + q_B + \omega q_A q_B$, where q_0 is the Boltzmann weight for promoter occupancy, q_A and q_B are the ratios of the regulatory protein concentrations to the binding thresholds for input A and input B, respectively, and ω is the mutual cooperativity factor.

42. (*New*) The method of claim 40, wherein the at least one selected logic function is OR, and $Z_{ON} = q_0(1 + \omega q_A + \omega q_B + 2\omega q_A q_B)$ and $Z_{OFF} = 1 + q_A + q_B + q_A q_B$, where q_0 is the Boltzmann weight for promoter occupancy, q_A and q_B are the ratios of the regulatory protein concentrations to the binding thresholds for input A and input B, respectively, and ω is the mutual cooperativity factor.

43. (*New*) The method of claim 40, wherein the at least one selected logic function is XOR, and $Z_{ON} = q_0(1 + \omega q_A + \omega q_B + 2\omega q_A q_B)$ and $Z_{OFF} = (1 + q_A + q_B + q_A q_B) \times (1 + q_A + q_B + \omega q_A q_B)$, where q_0 is the Boltzmann weight for promoter occupancy, q_A and q_B are the ratios of the regulatory

protein concentrations to the binding thresholds for input A and input B, respectively, and ω is the mutual cooperativity factor .

44. (*New*) The method of claim 40, wherein the at least one selected logic function is NAND, and $Z_{ON} = q_0$ and $Z_{OFF} = 1 + q_A + q_B + \omega q_A q_B$, where q_0 is the Boltzmann weight for promoter occupancy, q_A and q_B are the ratios of the regulatory protein concentrations to the binding thresholds for input A and input B, respectively, and ω is the mutual cooperativity factor.